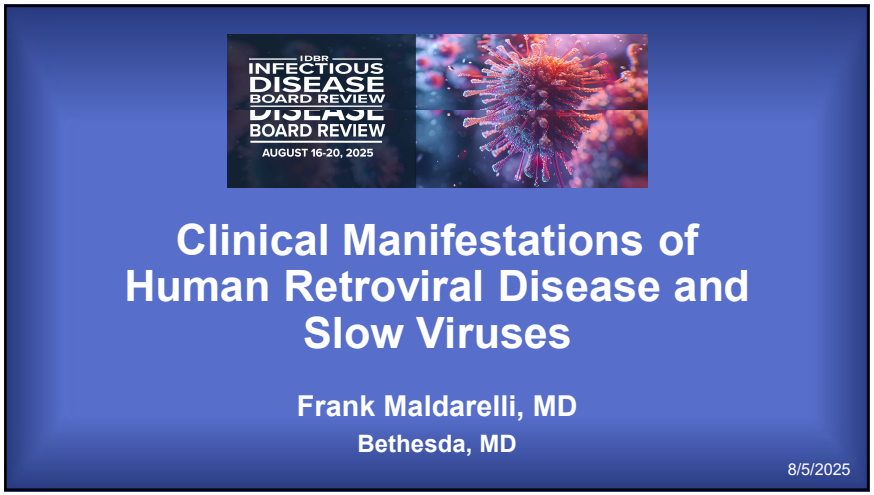
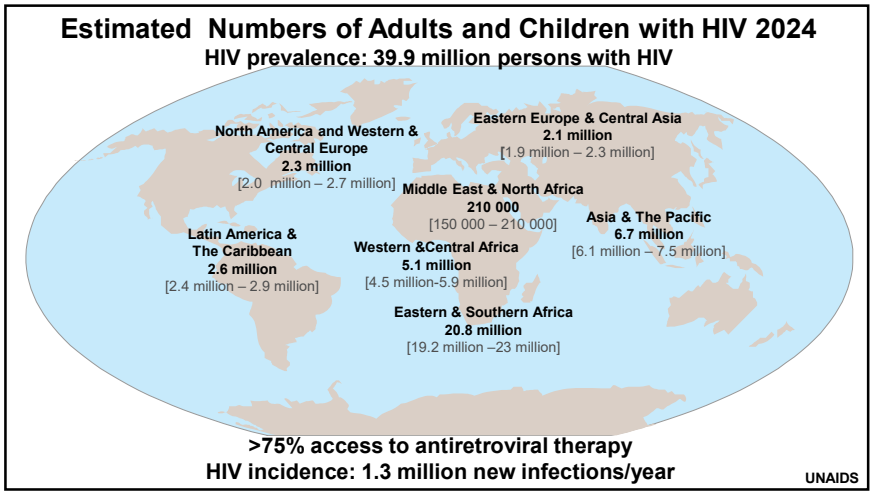
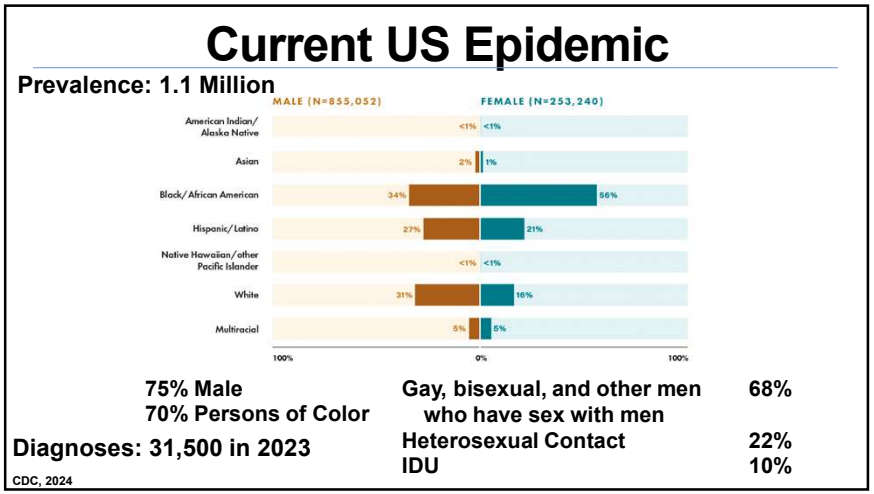


1

2



3



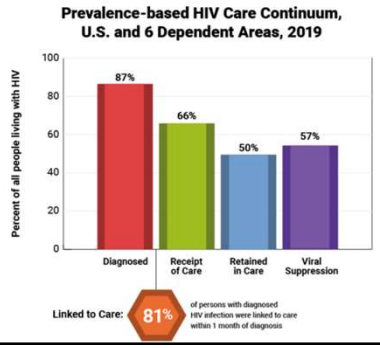
4

33 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

2030 US HIV Public Health Goals:Treatment Cascade

95% Diagnosed
95% Undergoing Antiretroviral Therapy
95% Viral RNA Suppressed



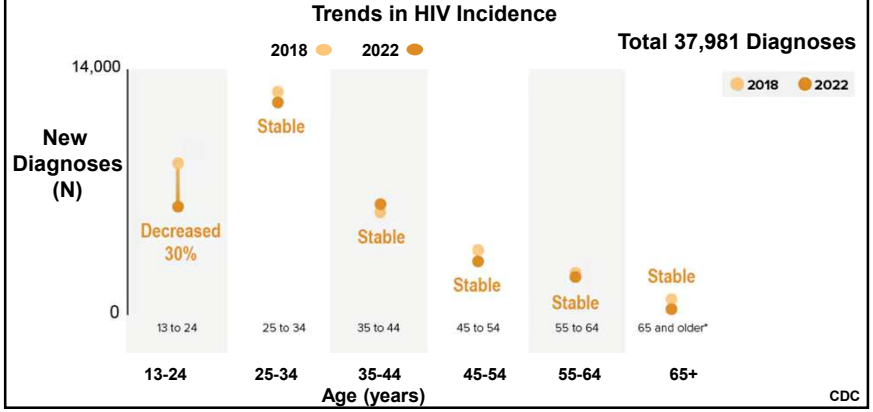
>50% Diagnoses are <35
>50% Living with HIV are>50 years

CDC

5

2030 US HIV Public Health Goals: Transmission

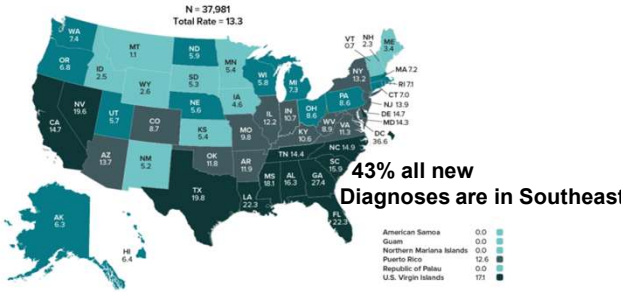
90% Reduction in Incidence by 2030



CDC

6

Trends in the US Epidemic: Geography: Shift South and Out of Metro Areas

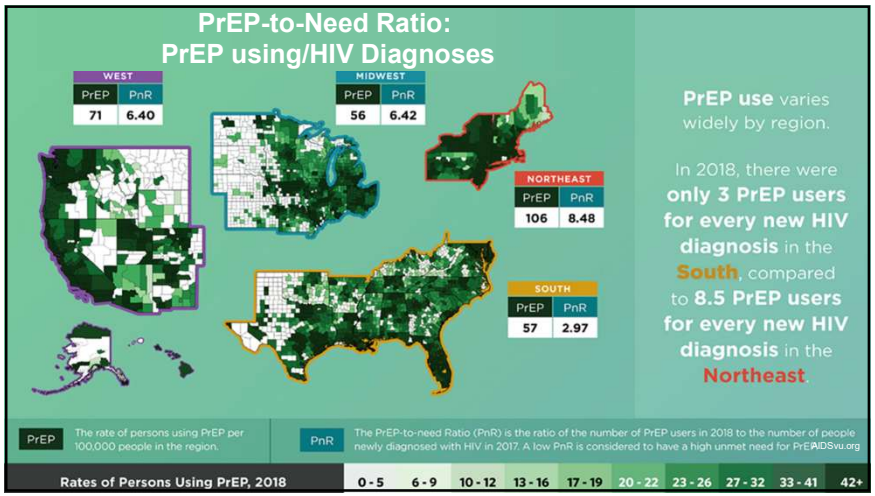


43% all new Diagnoses are in Southeast

Note. 2019 Data. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.
†Total estimate for the United States does not include data for Puerto Rico.

7

PrEP-to-Need Ratio: PrEP using/HIV Diagnoses

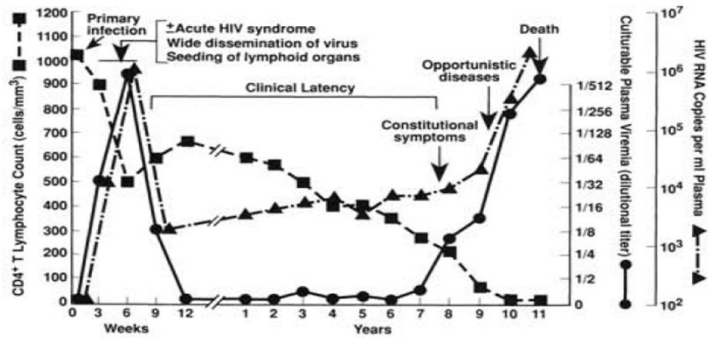


8

33 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Speaker: Frank Maldarelli, MD

HIV Infection Course



9

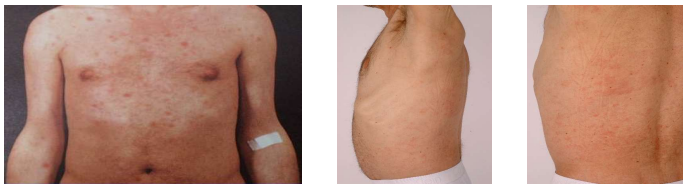
Acute HIV Syndrome

Sign/Symptom	Percent Reporting NEJM Review	Kenyan Sex Workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-27
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	2	nd	nd
Too ill to work	1	44	58

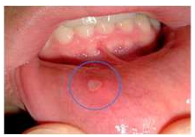
10

Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities



Enanthem



Aphthous ulcer

11

Question #1

A 23-year-old man presents with a history of unprotected receptive anal sex with known HIV-infected man, and one week of fever, diarrhea. HIV-1/2 ELISA is reactive, viral RNA level 500,000 c/ml. He is started immediately on antiretrovirals. His supplemental assay is negative, and repeat assays sent 3 weeks, 3 months, and one year after starting antiretrovirals are also negative.

ELISA is reactive. HIV-2 assay is negative. Viral RNA on therapy is <40 c/ml.

12

Question #1

Which of the following is correct explanation for the absence of positive results with the supplementary HIV test?

A. The patient was infected with a strain of HIV-1 that was not detected by the confirmatory assay
B. The patient is HIV-infected but did not develop a positive results with the supplementary assay because of the early antiretroviral therapy intervention
C. The patient never had HIV infection.
D. The patient had HIV but is now cured of HIV and antiretrovirals can safely be stopped

13

Early Antiretroviral Therapy

- Prompt reduction in HIV-1 RNA
- Potential blunting of humoral immune response
- Confirmatory assay may remain negative
- HIV-1 **DNA** PCR has been useful in documenting infection

14

Question #2

A 30-year-old individual who is completely adherent with long-acting cabotegravir as PrEP presents in January to your ED with low grade fever, fatigue, and mild myalgias. 4th generation HIV testing is non-reactive, rapid Flu A testing is negative.

15

Question #2

The ER physician asks whether this patient may have breakthrough HIV infection in the setting of PrEP, and whether further evaluation for HIV infection should be arranged.

A. The patient does not have breakthrough infections, because 4th generation assays are always reactive in the setting of breakthrough infection.
B. The patient does not have breakthrough infections, because breakthrough infections are always asymptomatic.
C. The patient may have breakthrough HIV infection, and further evaluation for HIV infection should be arranged.
D. The patient does not have breakthrough infections because breakthrough infections have never been reported with individuals completely adherent with long acting cabotegravir.

16

Long Acting Early Viral Inhibition (LEVI) Syndrome

- True breakthrough infection
- Smoldering presentation - symptoms may be present
- Serologic testing: seroconversion, seroreversion, "serowaffling" may persist for months
- Drug resistance to integrase inhibitor can emerge

17

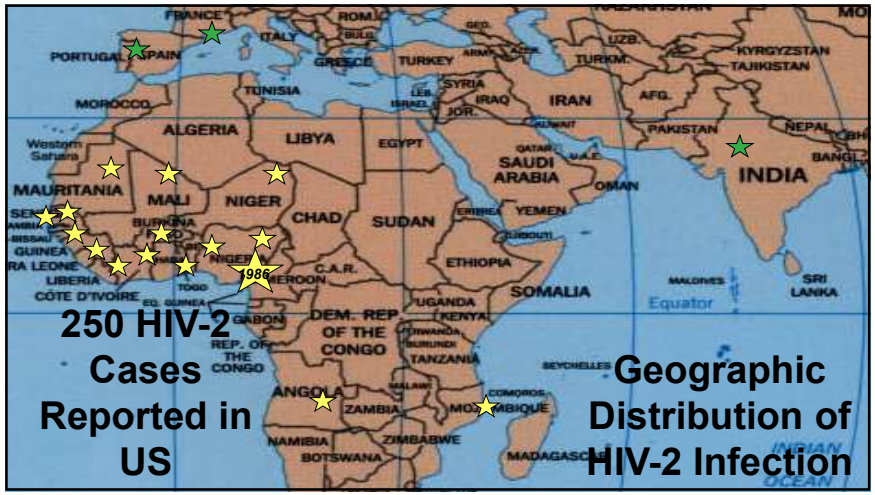
Question #3

A 49-year-old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius positive for HIV-2 and negative for HIV-1. CD4 cell count is 350 cells/μl.

Which of the following is correct?

A. HIV-2 is less pathogenic than HIV-1, and she only needs therapy with one antiretroviral drug
B. She should not be treated with protease inhibitors because HIV-2 is naturally resistant to PIs.
C. She should not be treated with NNRTI therapy because HIV-2 is naturally resistant to NNRTIs.
D. Use of routine HIV-1 viral load assays is useful in-patient management

18



19

HIV-1 and HIV-2

Characteristic	HIV-2	HIV-1
Epidemiology		
Geography	West/Centra Africa	Worldwide
Local Distribution	Urban=Rural	Urban>Rural
Age-Specific Prevalence	Stable or Decreasing	Increasing
Pathogenesis		
Average age at diagnosis	45-55	20-34
Maternal-fetal (without Rx)	0-4%	20-35%
Kaposi Sarcoma	Less common (10x)	More common
Therapy	NRTI, PI, INSTI, Corec	ALL antiretrovirals
Diagnosis	**NOT NNRTI, Fusion, (Capsid)**	
Screening	HIV 1/2 ELISA	HIV 1/2 ELISA
Confirmatory	Supplemental (e.g., Geenius)	Supplemental
Monitoring	HIV-2 RNA Assay	Qual. HIV RNA HIV-1 RNA Assay

20

Question #4

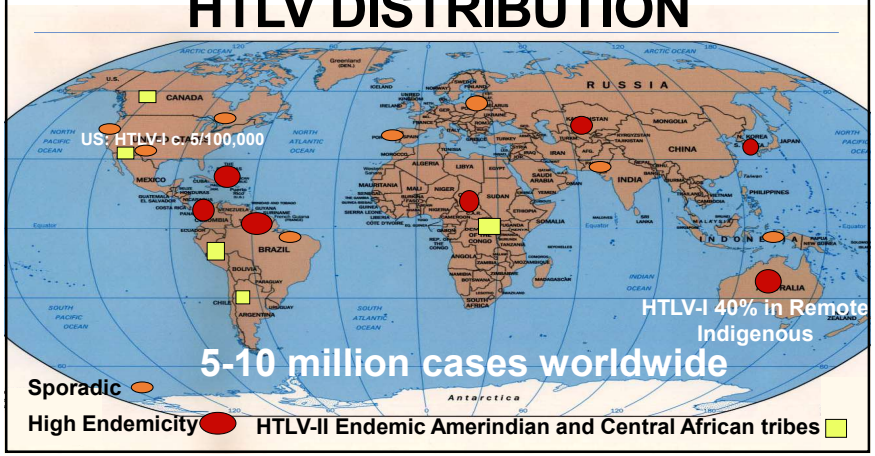
A 25-year-old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot.

Which of the following statements is true?

A. The risk of HTLV-I transmission can be entirely eliminated by caesarean section.
B. The risk of HTLV-I transmission will be entirely eliminated by not breastfeeding.
C. Breastfeeding will provide sufficient immunity to prevent infection with HTLV-I.
D. The risk of HTLV-I transmission will be significantly decreased but not entirely eliminated by avoiding breastfeeding.
E. There is no risk of HTLV-I disease. In this ethnic group, the HTLV-I test was likely a false positive.

21

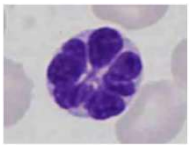
HTLV DISTRIBUTION



22

HTLV-I Transmission, Pathogenesis, Diagnostics

- Transmission
  - Breastfeeding
    - Prolonged duration: 20-30% seroconvert if breastfed >12 mos
    - High maternal HTLV proviral load in breastmilk: 28.7 infections/1000 person months with 1.5% HTLV+ lymphs
  - Sexual
  - Transfusion
    - Risk of seroconversion: 40-60%
- Pathogenesis
  - Spread to CD4+ T cells
    - 1-4% of all CD4 cells become infected - multilobed nuclei "flower cells"
    - Spread is NOT continuous, but controlled shortly after infection takes place
    - Infection maintained in CD4 by persistence and clonal expansion
- Laboratory diagnosis by sequential testing ELISA/Western blot FDA approved
  - Can distinguish HTLV-I from HTLV-II



Flower cell: HTLV-infected cell

23

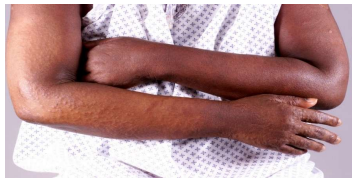
Question #5

37-year-old Jamaican female with diffuse pruritic rash (right), bone pain with lytic bone lesions.

WBC: 50,000, 90% lymphocytes

Which is most likely cause of her presentation?

A. HTLV-I
B. HTLV-II
C. HIV-1
D. HTLV-IV



24

HTLV-I Acute T cell Leukemia (ATL)

- **Disease Onset**
  - Long Latency (>30 years)
  - Small pediatric series in South America
- **Epidemiology**
  - Approximately 1% of HTLV- I infected adults
  - M>F (Japan); M=F (Jamaica)
- **Associated syndromes**
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - **Recurrent *Strongyloides***
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- **Therapy**
  - Cytotoxic chemotherapy
  - AZT+Ifn
  - Transplant
  - Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
    - APPROVED in Japan for ATL
    - In US FDA approved for relapsed or refractory Sezary or mycosis fungoides
  - Lenalidamide in trials

25

Question #6

38-year-old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence. Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex.

WBC = 7500 cells/µl
CD4 T cell = 1000 cells/µl
CSF cell count: 10 cells/mm3 (lymphocytes)
CSF protein: 75 mg/dl

26

Question #6

The etiologic agent associated with this illness is also associated with which of the following?

A. Acute T cell leukemia
B. Multiple sclerosis
C. Variant Creutzfeldt-Jacob
D. Hemorrhagic cystitis

27

HTLV-I Tropical Spastic Paraparesis /HTLV-1 Associated Myelopathy

- Epidemiology
  - <1% of HTLV-I develop HAM/TSP
  - The second most common neurologic syndrome in Jamaica after stroke
  - Latency may be short--several years
  - Female predominance

28

HTLV-I TSP/HAM

- Presentation
  - Spastic paraparesis
    - Lower>upper
    - Proximal>distal
  - Bladder disturbance
  - Hyperreflexia
  - Positive Babinski reflex
- Differential Diagnosis
  - Cord compression
  - B12 deficiency
  - Syphilis
  - HIV-1 myelopathy
  - Multiple sclerosis

29

Therapy of HTLV-I TSP/HAM

- Corticosteroids
  - May slow progression and reduce disability
- Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
- Teriflunomide in trials (FDA- Approved for MS; pyrimidine synthesis inhib)
- Antiretroviral therapy is NOT effective

30

Question #7

62-year-old woman from Jamaica recently diagnosed with multiple sclerosis who is now experiencing her first relapse and has been prescribed a course of natalizumab. She is also HTLV-1 seropositive; she has never had complications from HTLV, and you are consulted regarding treatment during therapy.

31

Question #7

Which of the following is most correct?

A. She is at risk for HTLV disease progression and should not be treated with natalizumab
B. She is not at risk for HLTV disease progression and can be treated with natalizumab.
C. She may be treated with natalizumab but should also be treated with antiretroviral therapy to prevent HTLV reactivation.
D. The HTLV serologic test may be false positive in multiple sclerosis, and she should first be tested for HTLV DNA, if she is DNA positive, she should not be treated with natalizumab.

32

Question #8

A 42-year-old man from the Haiti presents with fever, moderate respiratory distress, and nonproductive cough. HIV-1/2 ELISA is reactive, and discriminatory test is positive for HIV-1. A PCR test of the induced sputum is positive for *Pneumocystis jiroveci.* On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and the hematology technician remarks that some of the lymphocytes are "flower cells".

33

Question #8

Which of the following is most correct in explaining these findings?

A. The patient has HIV and B cell lymphoma
B. The patient has HIV infection and the elevated CD4 count is due to steroids used in the treatment of the *Pneumocystis* pneumonia
C. The patient has HTLV-1 infection only the HIV test is a false positive
D. The patient has both HIV infection and HTLV-1 infection

34

Question #9

A 56-year-old HTLV-I infected woman is diagnosed with multiple myeloma. She has never had complications from HTLV-I infection and is otherwise eligible for autologous bone marrow transplant. You are consulted regarding her eligibility for chemotherapy vs. chemotherapy and autologous bone marrow transplant.

35

Question #9

Which of the following is most correct?

A. She should not undergo autologous BMT because of reduced overall survival from ATL or other secondary malignancy in the post transplant period
B. She should not undergo autologous BMT because of the high risk of graft failure
C. She can undergo autologous BMT, but she should be treated with antiretroviral therapy from induction, until she recovers her counts (WBC>500 cells/µl)
D. She can undergo autologous BMT; her 3-year survival is equivalent to individuals without HTLV-I infection.

36

Pearls

HTLV-1 Infection

- Asymptomatic -95%
- Acute T cell Leukemia
- HAM/TSP
- But also
  - Bronchiectasis
  - Uveitis
  - Rheumatologic syndromes
  - Lymphocytic pneumonitis
  - Infective Dermatitis (pediatric)
- "Flower" cells
  - Lymphocytes with HTLV provirus present
  - Frequency in HIGHER in ATL and HAM/TSP
  - NOT an indication for specific therapy
- No indication for ART

Associated Infections

- *Strongyloides* hyperinfection
- Norwegian Scabies
- *Pneumocystis*
- MAC

HTLV-II

Not a cause of disease
A distractor

Thanks to Tamara Nawar, Ying Taur, Anna Kaltsas (SKMC, NYC)

37

SLOW VIRUSES

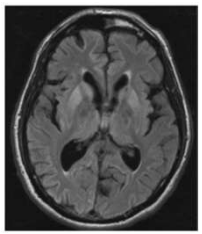
38

Question #10 (Prion Disease)

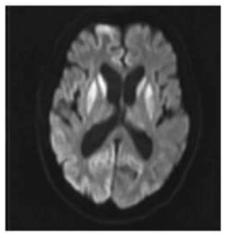
68-year-old butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

What is the most likely cause of the acquisition of this illness?

A. Contact with elk brains
B. Contact with sheep brains
C. Contact with pork brains
D. A spontaneous event



Flair



Diffusion Weighted Image

39

Prion Diseases: Transmissible Spongiform Encephalopathies

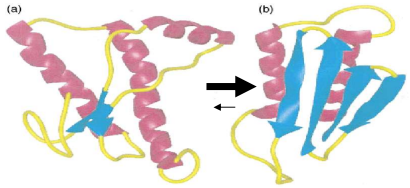
- **Spontaneous (N=~6000 worldwide per year)**
  - Sporadic Creutzfeldt-Jakob disease (sCJD)
- **Associated with specific exposure**
  - Ingestion of beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "vCJD" (N ~ 220 total cases)
      - Blood transfusion from individual with vCJD (4 cases)
  - Human brains
    - Kuru (N= ~2700 total cases)
- **Associated with a medical procedure (N ~ 450 total cases)**
  - Iatrogenic
  - Denoted "iCJD"
- **Hereditary (N ~600-900 worldwide per year)**
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)

40

Prion Disease Pathogenesis

A. Initiation

The prion protein is a host protein with a normal and abnormal conformation



NORMAL ABNORMAL

Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

41

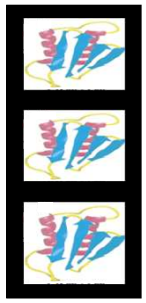
Prion Disease Pathogenesis

B. Propagation

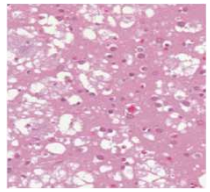
Protein-Protein Contacts recruit normal proteins into abnormal conformation

Prion Protein
Mutant Conformation

Direct Contact



Prion Protein
Mutant Conformation



Disaggregase chaperone proteins may scavenge these proteins with mutant conformation

42

Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

- Most Common Human Transmissible Spongiform Encephalopathy (TSE)
  - 95% cases
- Incidence estimated 1 per million
  - US: 0.1/million in <55 yo, 5.3/million >55 yo
  - Mean age of onset is 60 years

43

Dementia Comparison

Type	Protein	Clinical	Course	Path	MRI
sCJD	Prion	Myoclonus	<2 y	Spongif. Degen.	Caudate Striatum Thalamus
Alzheimer	Apo E4, Tau	Memory Language	>4 y	Neurofib. tangles	Hippocampus White matter
Lewy Body	α-Synuclein	Parkinsonian Visual hallucin.	>4 y	Lewy Bodies	Less common
Multi-infarct	Atheroma	Focal	Incremental	Vascular	Caudate,Pons Thalamus Ovoid Nuc

44

Question #11 (Prion Disease)

A 68-year-old man with dementia progressing over the last 6 months undergoes evaluation.

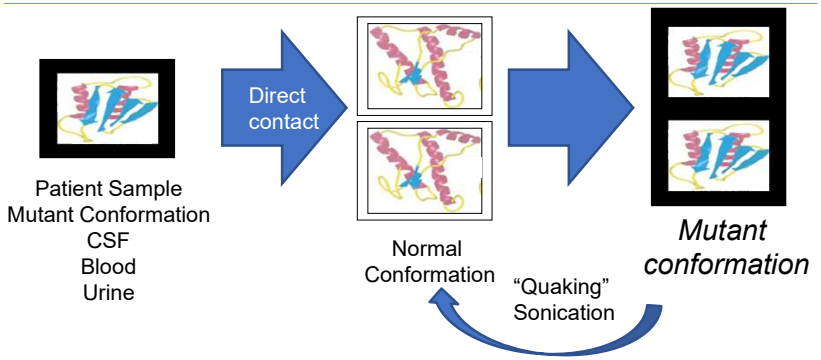
Which of the following CSF results is most consistent with Creutzfeldt Jakob Disease?

A. 14-3-3 protein: Positive
B. RT-QuIC: Positive
C. T-tau protein: 3000 pg/ml (normal 0-1150 pg/mL)
D. Aβ42: 1250 pg/mL (normal >1026 pg/mL)

45

Abnormal Prion Detection

RT-QuIC



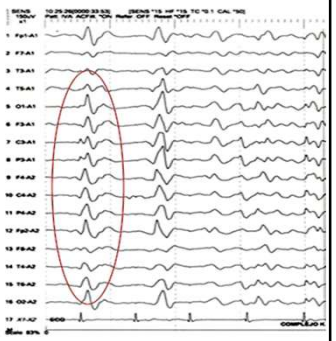
Sensitivity 92% Specificity >99%

46

Spontaneous Creutzfeldt-Jacob Disease (sCJD)

Typical Clinical Presentation

- Rapid progression
- RT-QuIC elevated abnormal prion protein
- Elevated Tau, 14-3-3 are supportive, but not specific for sCJD
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves



Herran, BMC Neurology 2018

47

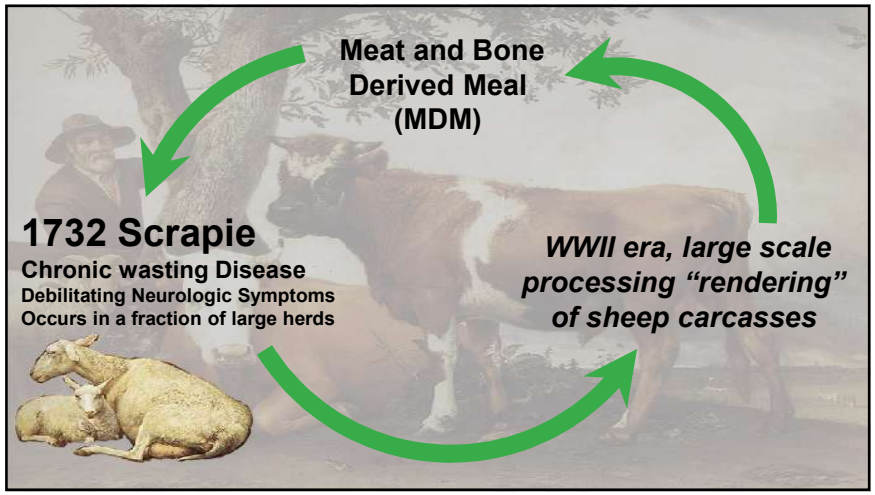
Question #12 (Prion Disease)

A 35-year-old man presents with dementia progressing over the last year. He was born in rural Indonesia, lived in London from 1985 - 2010, then moved to Philadelphia.

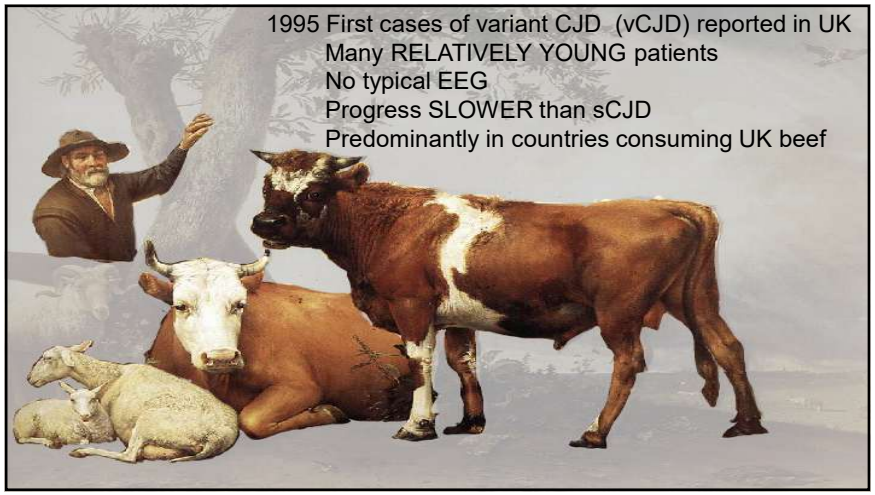
Which of the following diseases is most likely the cause of his symptoms?

A. Kuru
B. Variant Creutzfeldt-Jacob Disease
C. Familial Creutzfeldt-Jacob Disease
D. Rabies

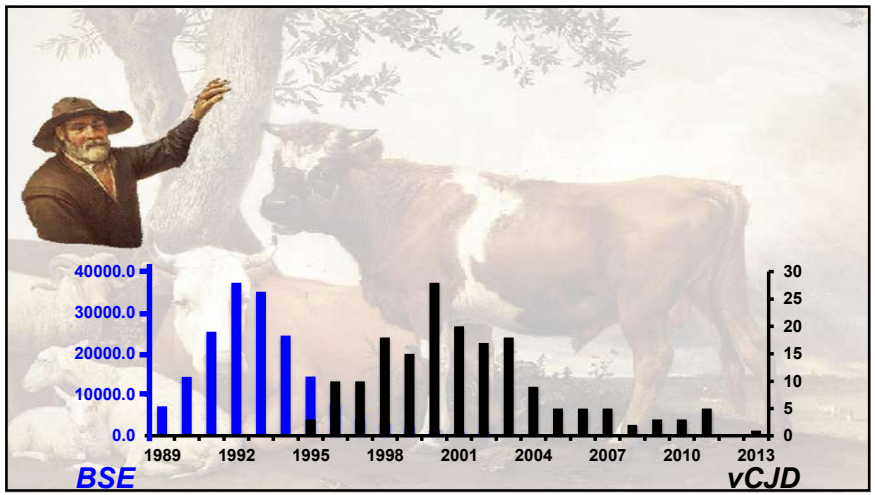
48



49



50



51

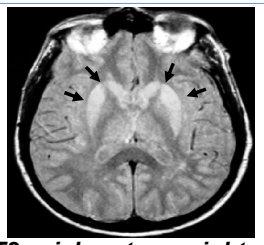
Numbers of vCJD Cases Worldwide

- United Kingdom: 177
- France: 26
- Spain: 5
- **US: 4**
  - **(ALL infections acquired OUTSIDE of US)**
- Ireland: 4
- Netherlands, Italy: 3
- Portugal, Canada, Italy: 2 each
- Saudi Arabia, Japan, Taiwan: 1 each

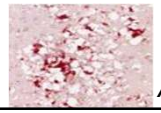
(https://www.ecdc.europa.eu/en/vcjd/ 2024)

52

sCJD

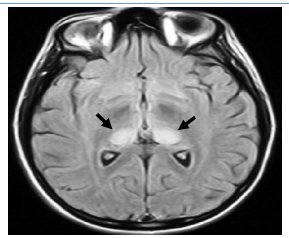


T2 axial proton weighted
Putamen and caudate head
"Double hockey stick sign"

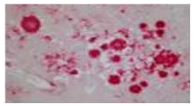


"Abnormal Prion Accumulation"

vCJD



T2 axial proton weighted
"Pulvinar Sign"
present >75% cases



"Florid Plaques"

53

Question #13 (Prion Disease)

A 49-year-old man recently emigrated from Japan presents with rapidly progressing dementia over the course of months. He underwent a meningioma resection with dura mater graft in Japan 35 years ago. He is an avid deer hunter and consumes venison.

What is the most likely cause of his dementia?

A. Iatrogenic CJD from the dura mater graft
B. CJD from eating deer
C. HTLV-I
D. Alzheimer's disease

54

Iatrogenic CJD ~450 cases

Definite Causes

- Pituitary extracts
  - Human Growth Hormone
  - Delay may be >30 y
- Dura mater grafts
  - Mostly Lyodura brand
- Transplants (RARE)
  - Corneal
  - Pericardium
  - Liver
- Instrumentation/Laboratory accident
  - Neurosurgeons Implantable Neurosurgical-implanted EEG, stereotactic procedures

No Link

- Vaccines
- Feces
- Saliva
- Sputum
- Bovine insulin
- Semen, vaginal secretions

55

CJD and Recommendations

- Patient
  - Detailed history
  - Blood/urine testing for presence of prions RT-QuIC
  - Referrals
  - Resources
- Family Members
  - Detailed history/Detailed discussion
  - No role for RT-QuIC routine screening for presence of prions in blood or urine
  - Genetic testing for prion variants may be useful
  - Referrals
  - Resources

56

Summary

	sCJD	iCJD	vCJD
Source	Spontaneous event	Human growth hormone Dura mater graft	Ingested beef
Distribution	Worldwide	Human growth hormone: US, Europe Dura mater graft: Japan	Linked to Beef originating largely in UK. US cases all have travel history
Median Age (y)	68	51	28
Progression	SHORTER	shorter	LONGER
EEG	Typically abnormal	few data but abnormal	NOT Typically abnormal
MRI (DWI)Basal ganglia	"Double Hockey Stick"	Few Data, Double Hockey Stick	"Pulvinar sign"
Pathology	Abnormal Prion Protein deposits	Abnormal Prion Protein deposits	"Florid Plaques"

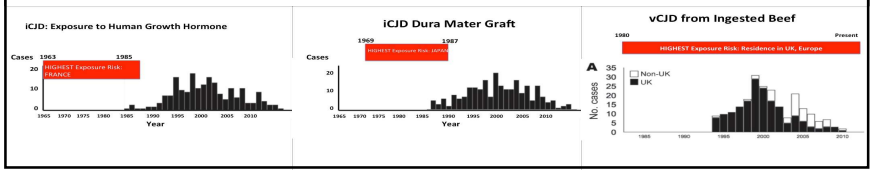
57

Prions Reference Material

58

Transmissible Spongiform Encephalopathy: Time and Place

Mode of transmission	Geographic Region	Risk Window
Beef ingestion	UK, France, Europe	1980-present
Human growth hormone	France	1963-1985
Dura mater graft	Japan	1969-1987



59

Kuru "Shivering, trembling"

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
  - Ambulant, leaning (pictured)
  - Sedentary
  - Terminal "laughing death"
  - "Florid plaques" (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991
- Last recorded case 2009

60

CJD and Blood Supply

- Transfusion-associated vCJD rarely documented (N=4, UK)
- NO documented transfusion-associated sCJD
- No FDA approved tests to detect transmission
- Deferral
  - Dura mater graft or human growth hormone
  - Donors with CJD or family history of CJD
  - Residence in Europe after 1980
  - Transfusion in Europe after 1980
  - Bovine insulin after 1980 unless certain that insulin was not from UK

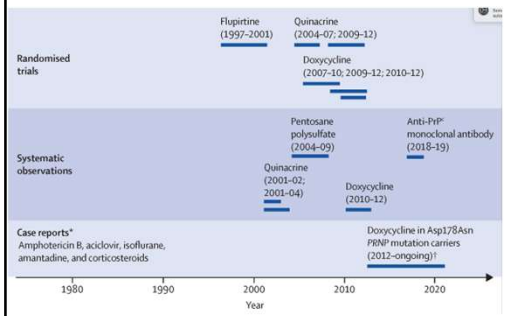
61

Transmissible Spongiform Encephalopathy
Infection Control Issues

- **Universal precautions**
- **No confirmed occupational transmissions**
  - CJD in health care workers occurs, occupational links have been suggested
- **Incinerate single use instruments**
- **Inactivate other instruments and materials**
  - 1N NaOH
  - Autoclave 121° C, 15 psi 30 min
  - Formic acid for tissue sections
  - Alternatives include hypochlorite (20,000 ppm chlorine) + autoclave
  - REMEMBER: Infectivity is STABLIZED by alcohol, formalin, or glutaraldehyde
- **WHO infection control guidelines**
  - http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf?ua=1

62

Transmissible Spongiform Encephalopathy
Multiple Trials but NO FDA Approved Therapy



PRN100 Antibody Under Study

- Anti-Prion antibody/G4 isotype
  - UK /J. Collinge/N=6
  - Achieved antibody levels in CSF
  - No disease reversal
  - ?Stabilization of rating scales

Future: Disaggregase Induction

Zerr, Lancet Neurology 2022

63

Resources

- **RT-QuIC: Case Western**
  - https://case.edu/medicine/pathology/divisions/national-prion-disease-pathology-surveillance-center/resources-professionals/contact-and-shipping-information
- **Diagnostic Criteria**
  - https://case.edu/medicine/pathology/research/national-prion-disease-pathology-surveillance-center/human-prion-diseases/diagnostic-criteria-creutzfeldt-jakob-disease-cjd
- **Epidemiology**
  - https://www.cdc.gov/prions/cjd/resources.html
- **Patient support**
  - https://cjdfoundation.org/other-resources
- **fmaldarelli3@gmail.com**

64